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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/397,550	09/16/99	BROWN J	A0000180-66-

HM12/0307

WARNER-LAMBERT COMPANY
2800 PLYMOUTH ROAD
ANN ARBOR MI 48105

EXAMINER	
MURPHY, J	
ART UNIT	**PAPER NUMBER**
1646	8

DATE MAILED: 03/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/397,550	BROWN ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) *8 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

~~APPLICANT COPY~~

DETAILED ACTION

Election/Restrictions

Claims 8 and 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7, 12/28/2000.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9 and 12 are rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for nucleotides encoding SEQ ID NO: 20 and 22, does not reasonably provide enablement for a nucleic acid encoding any other polypeptide. There is not adequate guidance as to the nature of the polypeptide which Applicants claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Claims 1, 9 and 12 are overly broad in the recitation of "alpha2delta-2" etc., since no guidance as to what constitutes " alpha2delta-2" etc. polypeptide is provided within the claims. The broad scope of claims 1, 9 and 12 can be read to encompass a polynucleotide encoding any isolated polypeptide. There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid encoding a polypeptide other than those

exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 1, 9 and 12 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 2-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 20 and 22, does not reasonably provide enablement for a polynucleotide encoding a substantially purified variant having at least 90% amino acid sequence identity to SEQ ID NO: 20 and 22. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2-3 and 5 is overly broad in the recitation of "at least 90% identical" since no guidance is provided as to which of the myriad of polynucleotide species encoding polypeptide species encompassed by the claim will retain the characteristics of a voltage-dependent calcium channel. The specification provides insufficient guidance how to generate voltage-dependent calcium channels, and does not disclosing any actual or prophetic examples on expected performance parameters of any of the possible muteins of voltage-dependent calcium channels. However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is insufficient guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid sequence encoding a voltage-dependent calcium channel other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 2-3 and 5 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7, 9 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9 and 12 are indefinite in that they only describe the peptide of interest by an arbitrary protein name, i.e. "alpha2delta-2" etc. There is nothing in the claims which distinctly identifies the protein. For example, others in the field may isolate the same protein and give said protein an entirely different name. Applicant should particularly point out and distinctly identify the polypeptide by claiming structural characteristics associated with the protein (e.g. amino acid sequence, molecular weight, etc.). Identification of biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly designate what that protein is.

Claims 7 and 9 recite the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids which might hybridize under conditions of moderate stringency, for example, would fail to hybridize under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification which Applicant considers to be "stringent".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al. (1998).

Wei et al. discloses a human alpha 2 calcium channel which is 100% identical to SEQ ID NO: 1 (See Sequence Comparison A, attached). This mRNA was cloned into a vector and expressed in host cells, thus anticipating claims 1, 4, and 10-12.

Claims 1, 6, 7, 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9504822 (Harpold et al.).

Harpold et al. discloses the cloning and expression of human voltage gated calcium channel subunits, thus anticipating claim 1. The polypeptide disclosed as neuronal alpha 2 polypeptide has regions of identity with the sequence disclosed in the instant application as SEQ ID NO: 20 (see Sequence Comparison B, attached, underlined region). Therefore a polynucleotide encoding the neuronal alpha 2 polypeptide has more than 10 consecutive nucleotides identical to SEQ ID NO: 19, thus anticipating claim 6. This polynucleotide would hybridize to SEQ ID NO: 19, thus anticipating claim 7. Nucleic acid probes are disclosed by Harpold et al. (page 12, first paragraph, thus anticipating claims 7 and 9. The polynucleotide encoding neuronal alpha 2 polypeptide was cloned into an expression vector and transfected into host cells, and the expressed protein was isolated (page 86-88), thus anticipating claims 10-12.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 5, 2001

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER

Sequence Comparison A

RESULT 1
AF042792
LOCUS AF042792 5463 bp mRNA PRI 17-JAN-1998
DEFINITION Homo sapiens alpha 2 delta calcium channel subunit isoform I mRNA, complete cds.
ACCESSION AF042792
VERSION AF042792.1 GI:2781438
KEYWORDS .
SOURCE human.
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 5463)
AUTHORS Wei,M.-H., Latif,F., Duh,F.-M., Adreazzoli-Angeloni,D., Kashuba,V., Zabarovsky,E., Johnson,B. and Lerman,M.I.
TITLE A new alpha 2 delta subunit of the L-type voltage gated calcium channel resides in the lung cancer critical region on 3p21.3
JOURNAL Unpublished
REFERENCE 2 (bases 1 to 5463)
AUTHORS Wei,M.-H., Latif,F., Duh,F.-M., Adreazzoli-Angeloni,D., Kashuba,V., Zabarovsky,E., Johnson,B. and Lerman,M.I.
TITLE Direct Submission
JOURNAL Submitted (12-JAN-1998) Laboratory of Immunobiology, National Cancer Institute, NCI-Frederick Cancer Research and Development Center, Bldg 560, Rm. 12-71, P.O.Box B, Frederick, MD 21702, USA
FEATURES Location/Qualifiers
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CDS 162. .3599
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YYDAKADAELDDPESEDVERGSKASTLRLDFIEDPNFKNKVNYSYAAVQIPTDIYKGS
TVILNELNWTEALENVFMENRRQDPTLLWQVFGSATGVTRYYPATPWRAPKKIDLYDV
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BASE COUNT 1211 a 1664 c 1501 g 1087 t
ORIGIN

Query Match 100.0%; Score 3186; DB 10; Length 5463;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 3186; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2202 CCCAGAGAGTACTGCAAGGACCTGAATGCCTCAGACAACAACACCGAGTTCCTGAAAAAC 2261

Qy   2101 tttattgagctcatggagaaagtgactccagactccaagcagtgcaacaacttccttctg 2160
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2262 TTTATTGAGCTCATGGAGAAAGTGACTCCAGACTCCAAGCAGTGCAACAACTTCCTTCTG 2321

Qy   2161 cacaacctgatcttggacacgggcatcacgcagcagctggtagagcgtgtgtggagggac 2220
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2322 CACAACCTGATCTTGGACACGGGCATCACGCAGCAGCTGGTAGAGCGTGTGTGGAGGGAC 2381
```

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Qy   2221 caggatctcaacacgtacagcctactggccgtgttcgctgccacagacggtggcatcacc 2280
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2382 CAGGATCTCAACACGTACAGCCTACTGGCCGTGTTCGCTGCCACAGACGGTGGCATCACC 2441

Qy   2281 cgagtcttccccaacaaggcagctgaggactggacagagaaccctgagcccttcaatgcc 2340
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2442 CGAGTCTTCCCCAACAAGGCAGCTGAGGACTGGACAGAGAACCCTGAGCCCTTCAATGCC 2501

Qy   2341 agcttctaccgccgcagcctggataaccacggttatgtcttcaagcccccacaccaggat 2400
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2502 AGCTTCTACCGCCGCAGCCTGGATAACCACGGTTATGTCTTCAAGCCCCCACACCAGGAT 2561

Qy   2401 gccctgttaaggccgctggagctggagaatgacactgtgggcatcctcgtcagcacagct 2460
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2562 GCCCTGTTAAGGCCGCTGGAGCTGGAGAATGACACTGTGGGCATCCTCGTCAGCACAGCT 2621

Qy   2461 gtggagctcagcctaggcaggcgcacactgaggccagcagtggtgggcgtcaagctggac 2520
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2622 GTGGAGCTCAGCCTAGGCAGGCGCACACTGAGGCCAGCAGTGGTGGGCGTCAAGCTGGAC 2681

Qy   2521 ctagaggcttgggctgagaagttcaaggtgctagccagcaaccgtacccaccaagaccag 2580
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2682 CTAGAGGCTTGGGCTGAGAAGTTCAAGGTGCTAGCCAGCAACCGTACCCACCAAGACCAG 2741

Qy   2581 cctcagaagtgcggccccaacagccactgtgagatggactgcgaggttaacaatgaggac 2640
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2742 CCTCAGAAGTGCGGCCCCAACAGCCACTGTGAGATGGACTGCGAGGTTAACAATGAGGAC 2801

Qy   2641 ttactctgtgtcctcattgatgatggaggattcctggtgctgtcaaaccagaaccatcag 2700
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2802 TTACTCTGTGTCCTCATTGATGATGGAGGATTCCTGGTGCTGTCAAACCAGAACCATCAG 2861

Qy   2701 tgggaccaggtgggcaggttcttcagtgaggtggatgccaacctgatgctggcactctac 2760
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2862 TGGGACCAGGTGGGCAGGTTCTTCAGTGAGGTGGATGCCAACCTGATGCTGGCACTCTAC 2921

Qy   2761 aataactccttctacacccgcaaggagtcctatgactatcaggcagcctgtgcccctcag 2820
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2922 AATAACTCCTTCTACACCCGCAAGGAGTCCTATGACTATCAGGCAGCCTGTGCCCCTCAG 2981

Qy   2821 ccccctggcaacctgggtgctgcaccccggggtgtctttgtgcccaccgttgcagatttc 2880
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   2982 CCCCCTGGCAACCTGGGTGCTGCACCCCGGGGTGTCTTTGTGCCCACCGTTGCAGATTTC 3041

Qy   2881 cttaacctggcctggtggacctctgctgccgcctggtccctgttccagcagcttctctac 2940
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   3042 CTTAACCTGGCCTGGTGGACCTCTGCTGCCGCCTGGTCCCTGTTCCAGCAGCTTCTCTAC 3101

Qy   2941 ggcctcatctaccacagctggttccaagcagaccccgcggaggccgaggggagccccgag 3000
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   3102 GGCCTCATCTACCACAGCTGGTTCCAAGCAGACCCCGCGGAGGCCGAGGGGAGCCCCGAG 3161

Qy   3001 acgcgcgagagcagctgcgtcatgaaacagacccagtactacttcggctcggtaaacgcc 3060
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   3162 ACGCGCGAGAGCAGCTGCGTCATGAAACAGACCCAGTACTACTTCGGCTCGGTAAACGCC 3221

Qy   3061 tcctacaacgccatcatcgactgcggaaactgctccaggctgttccacgcgcagagactg 3120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   3222 TCCTACAACGCCATCATCGACTGCGGAAACTGCTCCAGGCTGTTCCACGCGCAGAGACTG 3281

Qy   3121 accaacaccaatcttctctttgtggtggccgagaagccgctgtgcagccagtgcgaggct 3180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   3282 ACCAACACCAATCTTCTCTTTGTGGTGGCCGAGAAGCCGCTGTGCAGCCAGTGCGAGGCT 3341

Qy   3181 ggccgg 3186
          ||||||
Db   3342 GGCCGG 3347
```

Sequence Comparison B

```
RESULT   2
R71015
ID   R71015 standard; Protein; 1084 AA.
XX
AC   R71015;
XX
DT   01-DEC-1995  (first entry)
XX
DE   Human neuronal calcium channel subunit alpha 2e.
XX
KW   Calcium channel subunit; antagonist; agonist; diagnosis;
KW   Lambert Eaton Syndrome.
XX
OS   Homo sapiens.
XX
PN   WO9504822-A.
XX
PD   16-FEB-1995.
XX
PF   11-AUG-1994;   94WO-US09230.
XX
PR   11-AUG-1993;   93US-0105536.
PR   05-NOV-1993;   93US-0149097.
XX
PA   (SALK ) SALK INST BIOTECHNOLOGY IND ASSOC.
XX
PI   Ellis SB,  Gillespie A,  Harpold MM,  Mccue AF,  Williams ME;
XX
DR   WPI; 1995-090900/12.
DR   N-PSDB; Q84669.
XX
PT   DNA encoding human calcium channel sub-unit(s) - used for
PT   developing prods. for studying calcium channels, e.g. for
PT   obtaining agonists and antagonists
XX
PS   Disclosure; Page 248-253; 285pp; English.
XX
CC   Human neuronal alpha 2 coding sequence (Q84664) transcript is
CC   differentially processed in skeletal muscle, aorta, and CNS in
CC   the region corresp. to nt 1595-1942 of Q84664 in each of the
CC   tissues. Five alternatively spliced variant transcripts that differ
CC   in the presence or absence or one to three different portions of
CC   this region. There are three sequences involved (see Q84664 FT
CC   and Q84665 FT), sequence 1, sequence 2 and sequence 3. The five
CC   alpha 2 encoding transcripts from the different tissues include
CC   different combinations of the three sequences, except for one of
CC   the alpha 2 transcripts expressed in aorta which lacks all three
CC   sequences. The five alpha 2 forms identified are (1) a form that
CC   lacks sequence 3 called alpha 2a, expressed in skeletal muscle
CC   (2) one that lacks sequence 1 called alpha 2b, expressed in CNS
CC   (3) one that lacks sequences 1 and 2 called alpha 2c, expressed in
CC   aorta (4) one that lacks sequences 1, 2 and 3 called alpha 2d,
CC   expressed in aorta and (5) one that lacks sequences 1 and 3
CC   called alpha 2e. The DNA and AA sequences of alpha 2a - alpha 2e
CC   are set forth in Q84666-Q84669 and R71012-R71015 respectively.
XX
SQ   Sequence   1084 AA;


  Query Match             50.2%;  Score 3054;  DB 16;  Length 1084;
  Best Local Similarity   54.3%;  Pred. No. 5.1e-260;
  Matches  592;  Conservative  175;  Mismatches  292;  Indels   32;  Gaps   14;

Qy      44 LWLLLPLLPLLAAPGASAYSFPQQHTMQHWARRLEQEVDGVMRIFGGVQQLREIYKDNRN 103
           | | | |   |    :|   ||   |:: |  :::::  : :   || || :||:  ::
Db       7 laltltlfqslligpsseepfpsavtikswvdkmqedlvtlaktasgvnqlvdiyekyqd 66

Qy     104 LFEVQENEPQKLVEKVAGDIESLLDRKVQALKRLADAAENFQKAHRWQDNIKEEDIVYYD 163
           |: |: |  ::|||  | ||| ||  : :||  ||  ||  | ||:|:::    ::|||:
```

```
Db      67 lytvepnnarqlveiaardiekllsnrskalvslaleaekvqaahqwredfasnevvyyn 126

Qy     164 AKADAELDDPESEDVERGSKASTLRLDFIEDPNFKNKVNYSYAAVQIPTDIYKGSTVILN 223
           || |    |||  | | ||:   ::  |||| ||  :::| :||| ||||||:|||::||
Db     127 akddl---dpekndsepgsq--rikpvfiedanfgrqisyqhaavhiptdiyegstivln 181

Qy     224 ELNWTEALENVFMENRRQDPTLLWQVFGSATGVTRYYPATPW----RAPKKIDLYDVRRR 279
           ||||| ||: || :|| :||:||||||||||||: |||||:||    | | ||||||||||
Db     182 elnwtsaldevfkknreedpsllwqvfgsatglaryypaspwvdnsrtpnkidlydvrrr 241

Qy     280 PWYIQGASSPKDMVIIVDVSGSVSGLTLKLMKTSVCEMLDTLSDDDYVNVASFNEKAQPV 339
           |||||||:|||||:|:||||||||||||||::||| |||:||||||:|||||||  || |
Db     242 pwyiqgaaspkdmlilvdvsgsvsgltlklirtsvsemletlsdddfvnvasfnsnaqdv 301

Qy     340 SCFTHLVQANVRNKKVFKEAVQGMVAKGTTGYKAGFEYAFDQLQNSNITRANCNKMIMMF 399
           ||| |||||||||||| |:||  : ||| | || || :||:|| | |::|||||:||:|
Db     302 scfqhlvqanvrnkkvlkdavnnitakgitdykkgfsfafeqllnynvsrancnkiimlf 361

Qy     400 TDGGEDRVQDVFEKYNWPNRTVRVFTFSVGQHNYDVTPLQWMACANKGYYFEIPSIGAIR 459
           |||||:| |::| |||  :: |||| ||||||||:  |:|||||  |||||:|||||||||
Db     362 tdggeeraqeifnkyn-kdkkvrvfrfsvgqhnyergpiqwmacenkgyyyeipsigair 420

Qy     460 INTQEYLDVLGRPMVLAGKEAKQVQWTNVYEDALGLGLVVTGTLPVFNLTQ--DGPGEKK 517
           |||||||||||||||| :|||||||||| ||| ||||:|||||||:|   :     |
Db     421 intqeyldvlgrpmvlagdkakqvqwtnvyldalelglvitgtlpvfnitgqfenktnlk 480

Qy     518 NQLILGVMGIDVALNDIKRLTPNYTLGANGYVFAIDLNGYVLLHPNLKPQTTNFREPVTL 577
           |||||||||:||:| ||||||| :||  ||| |||| |||||||||:|:    :|||||
Db     481 nqlilgvmgvdvsledikrltprftlcpngyyfaidpngyvllhpnlqpknpksqepvtl 540

Qy     578 DFLDAELEDENKEEIRRSMIDGNKGHKQIRTLVKSLDERYIDEVTRNYTWVPIRSTNYSL 637
           ||||||||:: | |||  |||| | |  |||||| |||||:  | ||| |:  |:|||
Db     541 dfldaelendikveirnkmidgesgektfrtlvksqderyidkgnrtytwtpvngtdysl 600

Qy     638 GLVLPPYSTFYLQANLSDQILQVKYFEFLLPSSFESEGHVFIAPREYCKDLNASDNNTEF 697
            |||| || :|::| | : | | :| | | | :||  |: |||||:|| ||  |||||||
Db     601 alvlptysfyyikakleetitqarysetlkpdnfeesgytfiaprdycndlkisdnntef 660

Qy     698 LKNFIELMEKVTPDSKQCNNFLLHNLILDTGITQQLVERVWRDQDLNTYSLLAVFAATDG 757
           | || | ::: ||::  ||  |:: ::|| | | :||:  |  |  |   : | |  |||
Db     661 llnfnefidrktpnnpscnadlinrvlldagftnelvqnywskqk-nikgvkarfvvtdg 719

Qy     758 GITRVFPNKAAEDWTENPEPFNASFYRRSLDNHGYVFKPPHQDALLRPLELENDTVGILV 817
           |||||:| :| |:| |||| :  |||:|||||  |||  |: :    |   |:   ||:|
Db     720 gitrvypkeagenwqenpetyedsfykrsldndnyvftapyfnk-sgpgayes---gimv 775

Qy     818 STAVELSLGRRTLRPAVVGVKLDLEAWAEKFKVLASNRTHQDQPQKC-GPNSHCEMDCEV 876
           | |||: :  : |:|||||:|:|: :| | |      :|    |  | ||      ||:
Db     776 skaveiyiqgkllkpavvgikidvnswienf-----tktsirdp--cagp----vcdckr 824

Qy     877 NNEDLLCVLIDDGGFLVLSNQNHQWDQVGRFFSEVDANLMLALYNNSFYTRKESYDYQAA 936
           |:: : ||::||||||:::| :   :|:|||| |:| :||  | | | |   :|||||:
Db     825 nsdvmdcvilddggfllmanhddytnqigrffgeidpslmrhlvnisvyafnksydyqsv 884

Qy     937 CAPQPPGNLGAAPRGVFVPTVADFLNLAWWTSAAAWSLFQQLLYGLIYHSWFQADPAEAE 996
           | |      ||  |  :||:||| | : || :|||||: || |  | :    :|   | :
Db     885 cepgaapkqgaghrsayvpsvadilqigwwataaawsilqqfllsltfprlleavemedd 944

Qy     997 G-SPETRESSCVMKQTQYYFGSVNASYNAIIDCGNCSRLFHAQRLTNTNLLFVVAEKPLC 1055
             :    : ||: :||||:| : : |:: ::|||||||:|| ::| ||||:|:: |
Db     945 dftaslskqsciteqtqyffdndsksfsgvldcgncsrifhgeklmntnlifimveskgt 1004

Qy    1056 SQCEAGRLLQKETHCPADGPEQCELVQRPRYRRGPHICFDYNATEDTSDCGRGASFPPSL 1115
             |:   |:| |    :|||  |::|::||||:|| :||| |  || :|||  :   |||
Db    1005 cpcdtrlliqaeq--tsdgpnpcdmvkqpryrkgpdvcfdnnvledytdcggvsglnpsl 1062

Qy    1116 GVLVSLQLLLL 1126
             :: :| |||
Db    1063 wyiigiqflll 1073
```